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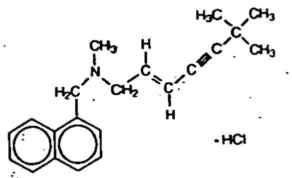
PHYSICIANS' DESK REFERENCE®

DESCRIPTION

Lamisil® (terbinafine hydrochloride tablets) Tablets contain the synthetic allylamine antifungal compound terbinafine hydrochloride.

Chemically, terbinafine hydrochloride is (E)-N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalenemethanamine hydrochloride. The empirical formula $C_{21}H_{26}ClN$ with a molecular weight of 327.90, and the following structural formula:



Terbinafine hydrochloride is a white to off-white fine crystalline powder. It is freely soluble in methanol and methylene chloride, soluble in ethanol, and slightly soluble in water.

Each tablet contains:

Active Ingredients: terbinafine hydrochloride (equivalent to 250 mg base)

Inactive Ingredients: colloidal silicon dioxide, NF; hydroxypropyl methylcellulose, USP; magnesium stearate, NF; microcrystalline cellulose, NF; sodium starch glycolate, NF

CLINICAL PHARMACOLOGY

Pharmacokinetics

Following oral administration, terbinafine is well absorbed (>70%) and the bioavailability of Lamisil® (terbinafine hydrochloride tablets) Tablets as a result of first-pass metabolism is approximately 40%. Peak plasma concentrations of 1 μg/mL appear within 2 h after a single 250 mg dose; the AUC (area under the curve) is approximately 4.56 μg•h/mL. An increase in the AUC of terbinafine of less than 20% is observed when Lamisil® is administered with food. No clinically relevant age-dependent changes in steady-state plasma concentrations of terbinafine have been reported. In patients with renal impairment (creatinine clearance ≤50 mL/min) or hepatic cirrhosis, the clearance of terbinafine is decreased by approximately 50% compared to normal volunteers. No effect of gender on the blood levels of terbinafine was detected in clinical trials. In plasma, terbinafine is >99% bound to plasma proteins and there are no specific binding sites. At steady-state, in comparison to a single dose, the peak concentration of terbinafine is 25% higher and plasma AUC increases by a factor of 2.5; the increase in plasma AUC is consistent with an effective half-life of ~36 hours. Terbinafine is distributed to the sebum and skin. A terminal half-life of 200-400 h may represent the slow elimination of terbinafine from tissues such as skin and adipose. Prior to excretion, terbinafine is extensively metabolized. No metabolites have been identified that have antifungal activity similar to terbinafine. Approximately 70% of the administered dose is eliminated in the urine.

Microbiology

Terbinafine hydrochloride is a synthetic allylamine derivative. Terbinafine hydrochloride is hypothesized to act by inhibiting squalene epoxidase, thus blocking the biosynthesis of ergosterol, an essential component of fungal cell membranes. *In vitro*, mammalian squalene epoxidase is only inhibited at higher (4000 fold) concentrations than is needed for inhibition of the dermatophyte enzyme. Depending on the concentration of the drug and the fungal species test *in vitro*, terbinafine hydrochloride may be fungicidal. However, the clinical significance of *in vitro* data is unknown.

Terbinafine has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the *INDICATIONS AND USAGE* section:

Trichophyton mentagrophytes
Trichophyton rubrum

The following *in vitro* data are available, but their clinical significance is unknown. *In vitro*, terbinafine exhibits satisfactory MIC's against most strains of the following microorganisms; however, the safety and efficacy of terbinafine in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials:

Candida albicans
Epidermophyton floccosum
Scopulariopsis brevicaulis

CLINICAL STUDIES

The efficacy of Lamisil® (terbinafine hydrochloride tablets) Tablets in the treatment of onychomycosis is illustrated by the response of patients with toenail and/or fingernail infections who participated in three US/Canadian placebo-controlled clinical trials.

Results of the first toenail study, as assessed at week 48 (12 weeks of treatment with 36 weeks follow-up after completion of therapy), demonstrated mycological cure, defined as simultaneous occurrence of negative KOH plus negative culture, in 70% of patients. Fifty-nine percent (59%) of patients experienced effective treatment (mycological cure [illegible] involvement or >[illegible] growth). [illegible] demonstrated mycological cure plus [illegible]ment).

[illegible] efficacy agains[illegible]

The pathogenic role of the non-dermatophytes cultured in the presence of dermatophytic onychomycosis has not been established. The clinical significance of this association is unknown.

Results of the fingernail study, as assessed at week 24 (6 weeks of treatment with 18 weeks follow-up after completion of therapy), demonstrated mycological cure in 79% of patients, effective treatment in 75% of the patients, and mycological cure plus clinical cure in 59% of the patients.

The mean time to overall success was approximately 10 months for the first toenail study and 4 months for the fingernail study. In the first toenail study, for patients evaluated at least six months after achieving clinical cure and at least one year after completing Lamisil® therapy, the clinical relapse rate was approximately 15%.

INDICATIONS AND USAGE

Lamisil® (terbinafine hydrochloride tablets) Tablets are indicated for the treatment of onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium) *(see DOSAGE AND ADMINISTRATION and CLINICAL STUDIES)*.

CONTRAINDICATIONS

Lamisil® (terbinafine hydrochloride tablets) Tablets are contraindicated in individuals with hypersensitivity to terbinafine or to any other ingredients of the formulation.

WARNINGS

Rare cases of symptomatic hepatobiliary dysfunction including cholestatic hepatitis have been reported. Treatment with Lamisil® (terbinafine hydrochloride tablets) Tablets should be discontinued if hepatobiliary dysfunction develops *(see PRECAUTIONS and ADVERSE REACTIONS)*.

There have been isolated reports of serious skin reactions (e.g., Stevens-Johnson Syndrome and toxic epidermal necrolysis). If progressive skin rash occurs, treatment with Lamisil® should be discontinued.

PRECAUTIONS

General

Changes in the ocular lens and retina have been reported following the use of Lamisil® (terbinafine hydrochloride tablets) Tablets in controlled trials. The clinical significance of these changes is unknown.

Hepatic function (hepatic enzyme) tests are recommended in patients administered Lamisil® (terbinafine hydrochloride tablets) Tablets for more than six weeks or in those who develop unexplained persistent nausea, anorexia, or fatigue or jaundice, dark urine, or pale stools *(see WARNINGS)*.

In patients with either pre-existing liver disease or renal impairment (creatinine clearance ≤50 mL/min), the use of Lamisil® has not been adequately studied, and therefore, is not recommended *(see CLINICAL PHARMACOLOGY, Pharmacokinetics)*.

Transient decreases in absolute lymphocyte counts (ALC) have been observed in controlled clinical trials. In placebo-controlled trials, 8/465 Lamisil®-treated patients (1.7%) and 3/137 placebo-treated patients (2.2%) had decreases in ALC to below 1000/mm^3 on two or more occasions. The clinical significance of this observation is unknown. However, in patients with known or suspected immunodeficiency, physicians should consider monitoring complete blood counts in individuals using Lamisil® therapy for greater than six weeks.

Isolated cases of severe neutropenia have been reported. These were reversible upon discontinuation of Lamisil®, with or without supportive therapy. If clinical signs and symptoms suggestive of secondary infection occur, a complete blood count should be obtained. If the neutrophil count is ≤1,000 cells/mm^3, Lamisil® should be discontinued and supportive management started.

Drug Interactions

In vitro studies with human liver microsomes showed that terbinafine does not inhibit the metabolism of tolbutamide, ethinylestradiol, ethoxycoumarin, and cyclosporine. *In vivo* drug-drug interaction studies conducted in normal volunteer subjects showed that terbinafine does not affect the clearance of antipyrine, digoxin, and the antihistamine terfenadine. Terbinafine decreases the clearance of intravenously administered caffeine by 19%. Terbinafine increases the clearance of cyclosporine by 15%.

Terbinafine clearance is increased 100% by rifampin, a CyP450 enzyme inducer, and decreased 33% by cimetidine, a CyP450 enzyme inhibitor. Terbinafine exposure (AUC) is increased 16% by terfenadine. Terbinafine clearance is unaffected by cyclosporine.

There is no information available from adequate drug-drug interaction studies with the following classes of drugs: oral contraceptives, hormone replacement therapies, hypoglycemics, theophyllines, phenytoins, thiazide diuretics, beta blockers, and calcium channel blockers.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 28-month oral carcinogenicity study in rats, a marginal increase in the incidence of liver tumors was observed in males at the highest dose level, 69 mg/kg/day (3.6× the Maximum Recommended Human Dose (MRHD) based on body surface area (BSA)). There was no dose-related trend and the mid-dose male rats (20 mg/kg/day; 1.0× the MRHD based on BSA) did not have any [illegible]. No increased incidence in liver tumors was noted in female rats at dose levels

A wide range of *in vivo* studies in mi[illegible] keys, and *in vitro* studies using ra[illegible] hepatocytes suggest that the develop[illegible] the high-dose male rats may be associ[illegible] proliferation, and support the conclu[illegible] specific finding. *In vivo* investigations [illegible] of the effects of Lamisil® on liver we[illegible] ultrastructure; hepatic cytochrome [illegible] proliferation assessed morphologicall[illegible] (peroxisomal enzymes) in mice, rats[illegible] The effects of Lamisil® and two know[illegible] patic morphology and peroxisomal [illegible] ities were also evaluated *in vivo* in mal[illegible] primary hepatocyte cultures from m[illegible] and from monkeys. The results of the [illegible] indicated that oral administration of La[illegible] day) resulted in peroxisome prolifera[illegible] these effects did not occur in mice, do[illegible] ther, *in vitro* studies indicated that pe[illegible] occurred in rat hepatocytes, but not i[illegible] hepatocytes.

Systemic exposure to Lamisil®, ass[illegible] state plasma unbound fraction area u[illegible] for terbinafine and metabolites, was [illegible] for male and female rats, respectivel[illegible] μg•h/mL for male and female mice, [illegible] comparable to the high doses in the ca[illegible] In human subjects at the MRHD (a da[illegible] Lamisil®), the unbound AUC was 0.[illegible] resulting safety margins for human[illegible] systemic exposure (AUC unbound), [illegible] 17 to 21 and 24 to 28, respectively.

The results of a variety of *in vitro* (m[illegible] *Salmonella*, DNA repair in rat hepato[illegible] Chinese hamster fibroblasts, chromos[illegible] sister chromatid exchanges in Chine[illegible] and *in vivo* (chromosome aberration[illegible] micronucleus test in mice) genotoxicit[illegible] dence of a mutagenic or clastogenic p[illegible] strated the absence of tumor-initiati[illegible] activity.

Oral reproduction studies in rats at d[illegible] day (approximately 12× the MRHD b[illegible] reveal any specific effects on fertility o[illegible] parameters. Intravaginal applicati[illegible] hydrochloride at 150 mg/day in pregna[illegible] crease the incidence of abortions or p[illegible] nor affect fetal parameters.

Pregnancy

Pregnancy Category B: Oral reproduc[illegible] performed in rabbits and rats at dose[illegible] (9× to 12× the MRHD, in rabbits [illegible] based on BSA) and have revealed n[illegible] fertility or harm to the fetus due to t[illegible] however, no adequate and well-contro[illegible] nant women. Because animal reprodu[illegible] always predictive of human respon[illegible] ment of onychomycosis can be pos[illegible] nancy is completed, it is recomme[illegible] initiated during pregnancy.

Nursing Mothers

After oral administration, terbina[illegible] milk of nursing mothers. The ratio [illegible] plasma is 7:1. Treatment with La[illegible] mended in nursing mothers.

Pediatric Use

The safety and efficacy of Lamis[illegible] lished in pediatric patients.

ADVERSE REACTIONS

The most frequently reported [illegible] the three US/Canadian placebo[illegible] in the table below. The adverse [illegible] gastrointestinal symptoms (inc[illegible] and abdominal pain), liver test [illegible] caria, pruritus, and taste distu[illegible] adverse events were mild, tra[illegible] discontinuation from study [illegible]

	[illegible] Adv[illegible]
	Lamis[illegible] (%) [illegible]
Headache	[illegible]
Gastrointestinal Symp[illegible]	[illegible]
Diarrhea	[illegible]
Dyspepsia	[illegible]
Abdominal Pain	[illegible]
Nausea	[illegible]
Flatulence	[illegible]
Dermatological Symp[illegible]	[illegible]
Rash	[illegible]
Pruritus	[illegible]
Urticaria	[illegible]

...bance	2...	...	0.2	0.0
...bance	1.1	1.5	0.9	0.0

...abnormalities ≥2× the upper limit of the ...

...ents, based on worldwide experience with ...afine hydrochloride tablets) Tablets use, in...matic idiosyncratic hepatobiliary dysfunction ...static hepatitis and very rarely liver failure) ...and PRECAUTIONS), serious skin reac...WARNINGS), severe neutropenia (see ...), thrombocytopenia and allergic reactions ...laxis). Uncommonly, Lamisil® may cause ...(including taste loss) which usually recov...al weeks after discontinuation of the drug. ...actions which have been reported include ...vomiting, arthralgia, myalgia, and hair ...

...effects reported spontaneously since the ...ed include altered prothrombin time (pro...duction) in patients concomitantly treated ...and Lamisil® (terbinafine hydrochloride ...and agranulocytosis (very rare).

...ence regarding overdose with Lamisil® ...rochloride tablets) Tablets is limited. Doses ...20 times the therapeutic daily dose) have ...inducing serious adverse reactions. The ...rdose included nausea, vomiting, abdomi...ss, rash, frequent urination, and headache.

...ADMINISTRATION

...afine hydrochloride tablets) Tablets, one ...hould be taken once daily for 6 weeks by ...ngernail onychomycosis. Lamisil®, one 250 ...ld be taken once daily for 12 weeks by pa...il onychomycosis. The optimal clinical ef...months after mycological cure and cessa.... This is related to the period required for ...lthy nail.

...ED

...ochloride tablets)

...e to yellow-tinged white circular, bi-convex, ...containing 250 mg of terbinafine imprinted ...in circular form on one side and code "250" ...

...ablets
...79-05
...lets
...78-15
...w 25°C (77°F); in a tight container. Protect ...

...euticals Canada, Inc.
...Canada H9S 1A9

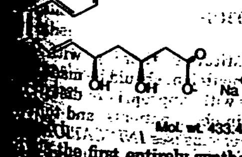
...uticals Corporation
...w Jersey 07936
...R 1999 T1999-71
...duct Identification Guide, page 325

℞

...ibing information is based on official ...uly 2000.

...sodium), is a water soluble cholesterol ...hich acts through the inhibition of ...lglutaryl-coenzyme A (HMG-CoA) ...

...[R*,S*-(E)]-(±)-7-[3-(4-fluorophenyl)-...indol-2-yl]-3,5-dihydroxy-6-heptenoic ...alt. The structural formula is:



Mol. wt. 433.46

...is the first entirely synthetic HMG-...und is in part structurally distinct ...ives of this therapeutic class. ...white to pale yellow, hygroscopic ...ethanol and methanol. Lescol®

	(range)	(range)	(range)	(range)	mean ± SD (range)
20 mg single dose (n=17)	166±106 (48.9-517)	207±65 (111-288)	0.9±0.4 (0.5-2.0)	107±38.1 (69.5-181)	2.5±1.7 (0.5-6.6)
20 mg b.i.d. (n=17)	200±86 (71.8-366)	275±111 (91.6-467)	1.2±0.9 (0.5-4.0)	87.8±45 (42.8-218)	2.8±1.7 (0.9-6.0)
40 mg single dose (n=16)	273±189 (72.8-812)	456±259 (207-1221)	1.2±0.7 (0.75-3.0)	108±44.7 (32.8-193)	2.7±1.3 (0.8-5.9)
40 mg b.i.d. (n=16)	432±236 (119-990)	697±275 (359-1559)	1.2±0.6 (0.5-2.5)	64.2±21.1 (25.7-111)	2.7±1.3 (0.7-5.0)

Median Percent Change in Lipid Parameters from Baseline to Week 24 Endpoint
All Placebo-Controlled Studies

	Total Chol.		TG		LDL		Apo B		HDL	
Dose	N	%Δ	N	%Δ	N	%Δ	N	%Δ	N	%Δ
All Patients										
Lescol 20 mg	747	-16.6	747	-11.9	747	-22.2	114	-19.3	747	+3.3
Lescol 40 mg	748	-18.6	748	-13.5	748	-25.0	125	-18.3	748	+4.4
Lescol 80 mg	257	-27.0	257	-17.8	257	-35.9	232	-28.4	257	+5.6
Baseline TG ≥200 mg/dL										
Lescol 20 mg	148	-16.4	148	-17.3	148	-21.6	23	-19.2	148	+5.8
Lescol 40 mg	179	-17.8	179	-19.6	179	-23.5	47	-18.3	179	+6.9
Lescol 80 mg	76	-26.8	76	-23.2	76	-34.6	69	-28.1	76	+9.0

(fluvastatin sodium) is supplied as capsules containing fluvastatin sodium, equivalent to 20 mg or 40 mg of fluvastatin, for oral administration.

Active Ingredient: fluvastatin sodium

Inactive Ingredients: gelatin, magnesium stearate, microcrystalline cellulose, pregelatinized starch, red iron oxide, sodium lauryl sulfate, talc, titanium dioxide, yellow iron oxide, and other ingredients.

May Also Include: benzyl alcohol, black iron oxide, butylparaben, carboxymethylcellulose sodium, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide and sodium propionate.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (Total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (a membrane transport complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-cholesterol (HDL-C) and its transport complex, apolipoprotein A, are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of Total-C and LDL-C and inversely with the level of HDL-C.

In patients with hypercholesterolemia, treatment with Lescol® (fluvastatin sodium) reduced Total-C, LDL-C, and apolipoprotein B. Lescol® (fluvastatin sodium) also moderately reduced triglycerides (TG) while producing an increase in HDL-C of variable magnitude. The agent had no consistent effect on either Lp(a) or fibrinogen. The effect of Lescol® (fluvastatin sodium)-induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity or mortality has not been determined.

Mechanism of Action

Lescol® (fluvastatin sodium) is a competitive inhibitor of HMG-CoA reductase, which is responsible for the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, a precursor of sterols, including cholesterol. The inhibition of cholesterol biosynthesis reduces the cholesterol in hepatic cells, which stimulates the synthesis of LDL receptors and thereby increases the uptake of LDL particles. The end result of these biochemical processes is a reduction of the plasma cholesterol concentration.

Pharmacokinetics/Metabolism

Oral Absorption

Fluvastatin is absorbed rapidly and completely following oral administration, with peak concentrations reached in less than 1 hour. Following administration of a 10 mg dose, the absolute bioavailability is 24% (range 9%-50%). Administration with food reduces the rate but not the extent of absorption. At steady-state, administration of fluvastatin with the evening meal results in a two-fold decrease in C_{max} and more than two-fold increase in t_{max} as compared to administration 4 hours after the evening meal. No significant difference in extent of absorption or in the lipid-lowering effects were observed between the two administrations. After single or multiple doses above 20 mg, fluvastatin exhibits saturable first-pass metabolism resulting in higher-than-expected plasma fluvastatin concentrations. The inactive enantiomer accounts for about 60% of the increase.

Distribution

Fluvastatin is 98% bound to plasma proteins. The mean volume of distribution (VD_{ss}) is estimated at 34.4 liters. The parent drug is targeted to the liver and no active metabolites are present systemically.

Metabolism

Fluvastatin is metabolized in the liver, primarily via hydroxylation of the indole ring at the 5- and 6-positions. N-dealkylation and beta-oxidation of the side-chain also occurs. The hydroxy metabolites have some pharmacologic activity, but do not circulate in the blood. Both enantiomers of fluvastatin are metabolized in a similar manner.

Elimination

Fluvastatin is primarily (about 90%) eliminated in the feces as metabolites, with less than 2% present as unchanged drug.

Special Populations

Renal Insufficiency: No significant (<6%) renal excretion of fluvastatin occurs in humans.

Hepatic Insufficiency: Fluvastatin is subject to saturable first-pass metabolism/sequestration by the liver and is eliminated primarily via the biliary route. Therefore, the potential exists for drug accumulation in patients with hepatic insufficiency. Caution should therefore be exercised when fluvastatin sodium is administered to patients with a history of liver disease or heavy alcohol ingestion (*see WARNINGS*).

Age: Plasma levels of fluvastatin are not affected by age.

Gender: Women tend to have slightly higher (but statistically insignificant) fluvastatin concentrations than men. This is most likely due to body weight differences, as adjusting for body weight decreases the magnitude of the differences seen.

Pediatric: No data are available. Fluvastatin is not indicated for use in the pediatric population.

Steady-state plasma concentrations show no evidence of accumulation of fluvastatin following administration of up to 80 mg daily, as evidenced by a beta-elimination half-life of less than 3 hours. However, under conditions of maximum rate of absorption (i.e., fasting) systemic exposure to fluvastatin is increased 33% to 53% compared to a single 20 mg or 40 mg dose.

Single-dose and steady-state pharmacokinetic parameters in 33 subjects with hypercholesterolemia are summarized below:

[See first table above]

Clinical Studies

Hypercholesterolemia (heterozygous familial and non familial) and Mixed Dyslipidemia

In 12 placebo-controlled studies in patients with Type IIa and IIb hyperlipoproteinemia, Lescol® (fluvastatin sodium) alone was administered to 1621 patients in daily dose regimens of 20 mg, 40 mg, and 80 mg (40 mg b.i.d.) for at least 6 weeks duration. After 24 weeks of treatment, daily doses of 20 mg, 40 mg, and 80 mg (40 mg b.i.d.) resulted in median LDL-C reductions of 22% (N=747), 25% (N=748) and 36% (N=257), respectively. Lescol® (fluvastatin sodium) treatment produced dose-related reductions in Apo B and in triglycerides and variable increases in HDL-C. In the subgroup of patients with primary mixed dyslipidemia, defined as baseline TG levels ≥200 mg/dL, treatment with Lescol® (fluvastatin sodium) also produced significant decreases in Total-C, LDL-C, TG and Apo B and variable increases in HDL-C.

In a long term open label free titration study, after 96 weeks LDL-C decreases of 25% (20 mg, N=68), 31% (40 mg, N=298) and 34% (80 mg, N=209) were seen. No consistent effect on Lp(a) was observed.

[See second table above]

Although frequently found in association with low HDL-C, elevated plasma TG has not been established as an independent risk factor for coronary heart disease. The independent effect of raising HDL-C or lowering TG on the risk for coronary and cardiovascular morbidity and mortality has not been established.

Atherosclerosis

In the Lipoprotein and Coronary Atherosclerosis Study (LCAS), the effect of Lescol® (fluvastatin sodium) therapy on coronary atherosclerosis was assessed by quantitative coronary angiography (QCA) in patients with coronary artery disease and mild to moderate hypercholesterolemia (baseline LDL-C range 115-190 mg/dL). In this randomized

Continued on next page